REMARKS

Claims 18-20 are pending in the application and are under consideration. Claim 20 has been amended to further clarify the intended subject matter of the claimed invention. No new matter is added by this amendment. Entry of this amendment is respectfully requested. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 18-22 are rejected under 35 U.S.C. § 112, first paragraph as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, page 3). These claims are directed to a genus of polynucleotides, including SEQ ID NO:2, a naturally-occurring human polynucleotide sequence variant encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, and complementary polynucleotides. In particular, it was asserted that "the claimed genus is extremely variable with the potential to encode proteins with widely variant functions," and that "a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claims" (Office Action, page 4). Claims 18 and 20, which are drawn to methods of detecting the recited polynucleotides of claim 19, are rejected as allegedly being "drawn to a method of use of a diverse genus." Claims 21 and 22 have been canceled, thus the rejections under 35 U.S.C. § 112 of these claims are moot. With respect to the other rejected claims, Applicants traverse for at least the reasons already made of record in Applicants' Brief on Appeal filed on November 26, 2001, and received in the Patent Office on January 18, 2002, and for the following reasons:.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published December 21, 1999 (Interim Guidelines), which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention[39], i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics[40]. What is conventional or well known to one skilled in the art need not be disclosed in detail[41]. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met[42].

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

Claim 20, as it is currently pending, recites "a probe comprising at least 60 contiguous nucleotides comprising a sequence **completely** complementary to SEQ ID NO:2." Support for this amendment can be found in the specification, for example, on page 21, lines 14-17, which describes the use of probes of at least about 60 nucleotides in length. Such a probe does not represent a diverse genus. It would be routine for one skilled in the art to use a probe "comprising at least 60 contiguous nucleotides comprising a sequence completely complementary to SEQ ID NO:2" to identify naturally-occurring variants encoding polypeptides with 90% identity to SEQ ID NO:1. The sequences of SEQ ID NO:1 and SEQ ID NO:2 are disclosed in the application, and the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and are described throughout the Specification of the instant application (for example, page 21, lines 10-17 and lines 27-30; page 22, lines 1-9; page 33, lines 13-30; page 34, lines1-3; page 43, lines, 7-25). One skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature.

For at least the above reasons, withdrawal of the written description rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Enablement rejections under 35 U.S.C. § 112, first paragraph

Claims 18 and 20-22 are rejected for allegedly failing to meet the requirements of 35 U.S.C. § 112, first paragraph, on the grounds that the Specification does not provide an enabling disclosure commensurate in scope with the claims (Office Action pages 5-7). In particular, the Examiner asserts that the specification "does not reasonably provide enablement for a method of use of a polynucleotide probe comprising 15, 30, or 60 nucleotides that are complementary to a polynucleotide of claim 19" (Office Action, page 5), and that "the specification does not support the broad scope of the claims which encompass all modifications and fragments of any sequence that comprises a fragment of SEQ ID NO:2 because the specification does not establish regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide encoded by a DNA of the instant invention"(Office Action, page 6). The Applicants traverse the rejection for at least the following reasons.

As a preliminary matter, claims 21 and 22 have been canceled in the present response. The rejections under 35 U.S.C. §112, first paragraph, of these claims is therefore moot, and should be withdrawn.

The first paragraph of 35 U.S.C. §112 requires that the Specification describe how to make and use the claimed subject matter. As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants submit that the disclosure amply enables the claimed invention. First, the specification describes, for example, specific assays for pyrophosphatase activity on page 44, lines 25-30, continuing on page 45, line, 1; binding assays to detect molecular interactions of "HPYP or biologically active fragments thereof' on page 46, lines 4-19; and immunological methods for detecting

and measuring HPYP on page 21, lines 18-26. These methods could be used to detect and characterize active and inactive peptide variants and fragments of SEQ ID NO:1. In addition, Figure 2 shows alignments of SEQ ID NO:1 with yeast and bovine pyrophosphatases, and points out regions of homology and conserved amino acid residues in the three proteins. In the specification, on page 11, lines 8-12, specific residues and motifs associated with pyrophosphatase catalytic activity are identified within SEQ ID NO:1.

Furthermore, the claims are directed to polynucleotides, not polypeptides, and it is the functionality of the claimed polynucleotides, not the polypeptides encoded by them, that is relevant. Members of the claimed genus of variants may include, for example, mutant alleles associated with diseases, or single nucleotide polymorphisms (SNPs). Members of the claimed genus of variants may be useful even if they encode defective HPYP polypeptides. For example, the variant polynucleotides could be used for the detection of sequences related to HPYP (see the specification a page 33, lines 13-25, and page 35, lines 16-21) including HPYP variants that may be associated with disease states, such as the diseases listed on page 34, lines 5-9, of the specification. See the specification at, for example, pages 34-35 for disclosure of how to use the claimed sequences in diagnostic assays.

Applicants also respectfully point out that the claims of the instant application are drawn to naturally-occurring variants. Thus it is not necessary to screen every conceivable variant which might be made using recombinant methods, as all that is claimed are those variant sequences which are found in nature. Given the sequences of SEQ ID NO:1 and SEQ ID NO:2, one of ordinary skill in the art could readily identify a naturally occurring polynucleotide encoding a polypeptide having at 90% identity to SEQ ID NO:1, using well known methods of sequence analysis, without any undue experimentation. The skilled artisan would also know how to use the claimed polynucleotides, for example in expression profiling, disease diagnosis, or detection of related sequences as discussed above.

The specification also describes the expression vectors into which the claimed fragments could be inserted, and the construction of fusion proteins (pages 17-19 and page 22, lines 10-30). Given this guidance, one of ordinary skill in the art would readily understand how to select and screen polynucleotides encoding fragments of SEQ ID NO:1 with pyrophosphatase activity or immunogenic activity without any undue experimentation.

For at least the above reasons, withdrawal of the enablement rejections of claims 18 and 20 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 18 and 20-22 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because the term "complementary" is defined in the specification (page 7, lines 2-10) by "non-limiting examples" (Office Action, page 8). It is stated that "absent specific definitions of the structure of a probe and/or specific hybridization conditions, it is impossible to know which structures are defined as a probe rendering the metes and bounds of the claim unascertainable." Claims 21 and 22 were canceled, thus rejection of these claims under 35 U.S.C. § 112, second paragraph is moot. The rejection of claims 18 and 20 is respectfully traversed for at least the following reasons.

Under the second paragraph of 35 U.S.C. § 112, the standard for "definiteness" is that the claims define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also MPEP § 706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonius v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir. 1983). The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph.

The term "hybridization" is defined in the specification at, for example, page 6, lines 21-22. The "specificity" of hybridization could be ascertained by one of skill in the art by considering the phrase "specifically hybridizes" in the context of claim 20. This claim recites a method of detecting a target polynucleotide, wherein the method relies upon the formation of a specific hybridization complex between a probe polynucleotide and the target polynucleotide. One of skill in the art would understand that the hybridization of the probe and target polynucleotides would require a certain degree of specificity in order to carry out the recited methods of detection. Furthermore, one of skill in the art would **reasonably** conclude that the degree of hybridization specificity is that which is necessary for operability of the recited methods. Therefore, a person of skill in the art would **reasonably** understand the metes and bounds of the phrase "specifically hybridizes" **in the context of the recited methods**.

Claim 20, as now amended, recites "a probe comprising at least 60 contiguous nucleotides comprising a sequence completely complementary to SEQ ID NO:2." This amendment further clarifies the structure of the probe and the scope of claim 20 and dependent claim 18.

For at least the above reasons, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

Rejections under 35 U.S.C. § 102(b)

Claims 18 and 20 were rejected under 35 U.S.C. § 102b and as "being anticipated" by Yang et al. (Office Action, page 8). Applicants respectfully disagree for at least the following reasons.

As a preliminary matter, the Examiner states that Yang *et al.* disclosed "a cDNA sequence that is more than 90% identical to SEQ ID NO:2 and comprises 15, 30, and 60 contiguous nucleotides thereof." See the Office Action at page 8. Applicants respectfully disagree about the extent of similarity alleged to exist between the two sequences. The Examiner's attention is directed to the enclosed Exhibits A and B, which show two different alignments of SEQ ID NO:2 with the cDNA sequence encoding bovine pyrophosphatase, performed using BLAST and CLUSTALW methods. Applicants respectfully point out that the sequence disclosed by Yang *et al.* and Applicants' SEQ ID NO:2 are less than 90% identical overall.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102(b), "the reference must teach every aspect of the claimed invention either explicitly or implicitly." M.P.E.P. § 706.02. Applicants respectfully submit that Yang *et al.* does not teach all aspects of Applicants invention, either explicitly or implicitly, as it is now claimed.

First, Claim 20 as it is currently pending recites "a probe comprising at least ***60*** contiguous nucleotides comprising a sequence ***completely complementary*** to SEQ ID NO:2" [emphasis added]. In contrast, there is no region of the reference sequence that exhibits 100% identity over 60 or more contiguous nucleotides of Applicants' SEQ ID NO:2.

Further, Claim 20 as it is currently pending also recites "a method of detecting a target polynucleotide in a sample, said target polyucleotide having the sequence of a polynucleotide of claim 19." However, the reference of Yang *et al.* does not disclose either SEQ ID NO:2 or any sequence that is at least 90% identical to it overall. Therefore, the target sequence of Applicants' claimed method is not disclosed by the reference.

Since Yang *et al.* does not explicitly teach the nucleotide sequence of SEQ ID NO:2, this reference must teach the sequence of SEQ ID NO:2 implicitly in order to be used as the basis for a rejection under 35 U.S.C. § 102(b). The Office must provide a rationale or evidence tending to show that the properties of the claimed subject matter are inherent in the references used in an anticipation rejection. "The fact that a certain result or characteristic **may** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." M.P.E.P. § 2112 (emphasis in original). "[T]he examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art." *Id.* (emphasis in original).

In the present case, the Office has in effect asserted that the sequence of SEQ ID NO:2 is inherent in the teachings of Yang et al. However, the Office has not provided any convincing proof--or any evidence whatsoever-- that this is in fact the case.

Therefore, because the rejection of claims 18 and 20-22 under 35 U.S.C. § 102(b) is improper for at least the preceding reasons, withdrawal of that rejection is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 18 and 20 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang *et al.* In particular, the Office Action alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a polynucleotide described by Yang *et al.* to detect a polynucleotide of claim 19 in a sample comprising polynucleotides prepared from human tissue (Office Action, page 9). This rejection is respectfully traversed for at least the following reasons.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02.

In the present case, the rejection of claims 18 and 20 under 35 U.S.C. § 103(a) is based on the allegation that Yang *et al.* anticipate the polynucleotides recited by claim 19. However, as previously discussed, the Yang *et al.* reference does not explicitly teach the claimed target sequences (i.e. the

polynucleotide sequence of SEQ ID NO:2, variants encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, and complements of these sequences). Applicants again note that the polynucleotide of Yang et al. has less that 90% sequence identity to a portion of SEQ ID NO:2 (see Exhibits A and B) and does not encode the same protein.

Further, as was also discussed above, these references do not anticipate the claimed polynucleotides because the disclosed polynucleotides encoding pyrophosphatases are not **necessarily** the same as the claimed polynucleotides. "The fact that a certain result or characteristic **may** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." M.P.E.P. § 2112 (emphasis in original). "[T]he examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art." *Id.* (emphasis in original).

Therefore each and every limitation of the claims is not found in the prior art, and a proper rejection under 35 U.S.C. § 103 cannot be made.

Moreover, Applicants also respectfully point out that the assertion that the existence of a polynucleotide with partial homology to the claimed polynucleotides renders methods of detecting the polynucleotides obvious is clearly contradictory to existing precedent. See *In re Bell* 26 U.S.P.Q.2d, 1529 (Fed. Cir. 1993); *In re Deuel* 34 U.S.P.Q.2d, 1210 (Fed. Cir. 1995)), which makes clear that knowledge of a general method for a making a compound does not render obvious the specific compound so produced. "A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search." (*Deuel*).

In sum, there has been no convincing showing of how the teachings of Yang et al. could be modified in order to arrive at the claimed subject matter, nor has convincing evidence that the claimed polynucleotides **necessarily** flow from this reference been provided. Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

For at least the above reasons, these rejections should be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Please charge Deposit Account No. **09-0108** in the amount of **$ 110.00** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. **09-0108.**

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 21 and 22 have been canceled.

Claim 20 has been amended as follows:

20. (Once Amended) A method of detecting a target polynucleotide in a sample, said target polyucleotide having the sequence of a polynucleotide of claim 19, comprising

hybridizing the sample with a probe comprising at least 60 [15] contiguous nucleotides comprising a sequence completely complementary to SEQ ID NO:2 [said target polynucleotide in the sample], and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and

detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.